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Dopamine transporter binding in symptomatic controls and healthy volunteers: Considerations for neuroimaging trials

Emma A. Honkanen [a,b,c,*], Mikael Eklund [a,c], Simo Nuuttila [a], Tommi Noponen [d,e], Elina Jaakkola [a], Elina Mäkinen [a], Risto Hirvilammi [d,e], Marko Seppänen [d], Kari Lindholm [a], Filip Scheperjans [f], Riitta Parkkola [g], Juho Joutsa [a,c,h], Andrea Varrone [i], Valtteri Kaasinen [a]

[a] Clinical Neurosciences, University of Turku and Turku University Hospital, Turku, Finland
[b] Department of Neurology, Satasairaala Central Hospital, Pori, Finland
[c] Turku PET Centre, Turku University Hospital, Turku, Finland
[d] Department of Clinical Physiology and Nuclear Medicine, University of Turku and Turku University Hospital, Turku, Finland
[e] Department of Medical Physics, Turku University Hospital, Turku, Finland
[f] Department of Neurology, Helsinki University Hospital and Department of Clinical Neurosciences (Neurology), University of Helsinki, Helsinki, Finland
[g] Department of Radiology, University of Turku and Turku University Hospital, Turku, Finland
[h] Turku Brain and Mind Center, University of Turku, Turku, Finland
[i] Department of Clinical Neuroscience, Centre for Psychiatry Research, Karolinska Institutet and Stockholm Health Care Services, Stockholm, Sweden

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ABSTRACT

Objective: To evaluate possible differences between brain dopamine transporter (DAT) binding in a group of symptomatic parkinsonism patients without dopaminergic degeneration and healthy individuals.
Background: Dopaminergic neuroimaging studies of Parkinson's disease (PD) have often used control groups formed from symptomatic patients with apparently normal striatal dopamine function. We sought to investigate whether symptomatic patients can be used to represent dopaminergically normal healthy controls.
Methods: Forty healthy elderly individuals were scanned with DAT [^{123}I]FP-CIT SPECT and compared to 69 age- and sex-matched symptomatic patients with nondegenerative conditions (including essential tremor, drug-induced parkinsonism and vascular parkinsonism). An automated region-of-interest based analysis of the caudate nucleus and the anterior/posterior putamen was performed. Specific binding ratios (SBR = [ROI-occ]/occ) were compared between the groups.
Results: DAT binding in symptomatic patients was 8.6% higher in the posterior putamen than in healthy controls ($p = 0.03$). Binding correlated negatively with age in both groups but not with motor symptom severity, cognitive function or depression ratings.
Conclusions: Putaminal DAT binding, as measured with [^{123}I]FP-CIT SPECT, was higher in symptomatic controls than in healthy individuals. The reason for the difference is unclear but can include selection bias when DAT binding is used to aid clinical diagnosis and possible self-selection bias in healthy volunteerism. This effect should be taken into consideration when designing and interpreting neuroimaging trials investigating the dopamine system with [^{123}I]FP-CIT SPECT.

1. Introduction

Neuroimaging trials that attempt to mechanistically explain disease processes typically involve a control group that represents normality. Often, control groups are formed of age- and sex-matched healthy individuals, but in many reported dopaminergic neuroimaging studies focusing on Parkinson's disease (PD), control groups comprise other symptomatic patients with normal tracer binding (e.g., Catafau et al., 2004; Gaenslen et al., 2008; Kaasinen et al., 2014; Badoud et al., 2016). Symptomatic controls have usually been retrospectively selected from groups of patients who have undergone diagnostic imaging due to clinically uncertain parkinsonian syndromes.

The purpose of the present study was to investigate the validity of clinical cohorts as controls in dopamine transporter (DAT) imaging and

* Corresponding author: Division of Clinical Neurosciences, Turku University Hospital POB 52, FIN-20521 Turku, Finland.
E-mail address: ealhonk@utu.fi (E.A. Honkanen).

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identify possible weaknesses in this approach. We therefore scanned healthy subjects with DAT single photon emission computed tomography (SPECT) and compared them to a group of symptomatic patients with apparently normal DAT imaging results.

2. Methods

2.1. Subjects

The inclusion criteria for healthy controls (n = 40) were age 50–85 years, no medications affecting the central nervous system, and no neurological symptoms or relevant prior neurological or psychiatric diseases. The participants were scanned with [123I]N-ω-fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl)nortropane ([^{123}I]FP-CIT) SPECT and brain structural magnetic resonance imaging (MRI) on the same day. MR imaging was performed with a Siemens 3 T Skyra Fit system (Siemens Medical Imaging, Erlangen, Germany) and the imaging protocol included three-dimensional T1, T2 and FLAIR images. Age- and sex-matched symptomatic patients (n = 69) were selected from a sample of 269 patients who had been scanned with [^{123}I]FP-CIT SPECT because of parkinsonism or tremor of unknown origin. Data were collected between 2014 and 2019. All patients had undergone structural brain imaging (MRI or CT) prior to SPECT. The exclusion criteria were degenerative parkinsonism (PD, multiple system atrophy (MSA), progressive supranuclear palsy (PSP), corticobasal syndrome (CBS)), dementia (Lewy body dementia (LBD), Alzheimer's disease (AD), frontotemporal dementia (FTD)) or undetermined diagnosis after a mean clinical follow-up of 3.4 (standard deviation (SD) 1.6) years after SPECT imaging.

All subjects were clinically examined 2–4 h before DAT imaging. The investigation included a clinical interview, the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part III, the Mini-Mental State Examination (MMSE), the Beck Depression Inventory (BDI), Beck Anxiety Inventory (BAI), the Barratt Impulsiveness Scale (BIS-11) (Patton et al., 1995), the single-question screen for REM sleep behavior disorder (RBD) (Postuma et al., 2012) and the Non-Motor Symptoms Scale (NMSS) (Chaudhuri et al., 2007). All participants gave written informed consent to participate in the study. The study was approved by the local Ethics Committee and was conducted according to the Declaration of Helsinki.

For additional analyses, symptomatic patients were divided to subgroups according to their diagnoses: essential tremor (ET), drug-induced parkinsonism (DIP) and vascular parkinsonism (VP). Also, additional analyses were performed by excluding healthy controls with a positive family history of PD, because it is a known risk factor for PD (Jacobs et al., 2020) and individuals with a positive family history could thus have higher likelihood of having prodromal PD. As DIP or the intake of selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) or VP may affect the [^{123}I]FP-CIT binding (Ba and Martin, 2015), these patients were excluded in subanalyses in order to rule out artificially decreased binding in the occipital cortex.

2.2. SPECT imaging

To prevent radiation exposure of the thyroid tissue, 250–300 mg of potassium perchlorate or Jodix™ (potassium iodide) 130 mg tablet was given 30–60 min before the tracer injection. The injected activity of [^{123}I]FP-CIT was 185 MBq, and the radiopharmaceutical was administered using a slow 20-s intravenous injection. The image acquisition started 3 h after the injection.

Patients were scanned using one of our two GE Infinia II Hawkeye SPECT/CT systems (GE Healthcare, Tirat Hacarmel, Israel) or Siemens Symbia T6 (Siemens Healthineers, Erlangen, Germany) SPECT/CT system. All healthy controls were scanned using Symbia T6. All SPECT/CTs are dual-head systems with low-energy high-resolution collimators. Patients were positioned to lie supine, and the camera heads were manually adjusted close to patient's head in a circular orbit. For the GE Infinia, the energy window was 159 keV ± 10 % and for the Symbia 159 keV ± 5 %. For all systems, the acquisition matrix size was 128x128, the rotation arc was 180° in step-and-shoot mode, and the angular step was 3°, resulting in 60 projections for each camera head and a total of 120 projections. The acquisition zoom was 1.23–1.28 and the time per projection was 35 s.

2.3. SPECT reconstruction and BRASS analysis

SPECT images were reconstructed using a three-dimensional (3D) ordered-subsets expectation maximization (OSEM) reconstruction algorithm (HybridRecon Neurology, version 1.3, Hermes Medical Solutions AB, Stockholm, Sweden), with 15 iterations, 5 subsets, uniform attenuation correction with the attenuation coefficient of 0.146 1/cm, collimator response correction using Gaussian diffusion model, Monte-Carlo-based scatter correction for the ^{123}I isotope and 3D Gaussian postfiltering with a full-width-at-half-maximum of 0.7 cm. The reconstructed images were analyzed using BRASS analysis software (version 2.6, Hermes Medical Solutions, Stockholm, Sweden).

Before the first subject was scanned, all SPECT systems were similarly calibrated using a striatal phantom to minimize the effect of sensitivity and partial volume effect variations between the systems on the acquired data (Tossici-Bolt et al., 2011; Diemling, 2012). The system-specific calibration coefficients were then implemented into BRASS software. With BRASS software, the SBRs of DAT binding were calculated with six striatal regions of interests (ROIs) (the right and left anterior putamen, the right and left posterior putamen, the right and left caudate nucleus), which were automatically segmented. The occipital cortex was used as the reference region and the SBRs were calculated as: SBR = (ROI – ROIoccipital)/ROIoccipital (Varrone et al., 2013). Posterior putamen DAT binding asymmetry index was calculated (with following formula: right – left posterior putamen SBR/ right + left posterior putamen SBR) (Kaasinen, 2016) and compared between the groups. Occipital cortex radioactivity values were calculated to compare reference region binding between groups (Joutsa et al., 2015) and to investigate possible effects of aminergic medications and vascular lesions on reference region binding.

2.4. Statistical analyses

SPSS Statistics (IBM version 26, SPSS Inc., Chicago, IL, USA) was used for all statistical analyses. The assumption of normality was tested with Shapiro-Wilk tests together with histograms. The differences between the groups were calculated using independent samples *t*-test, Mann-Whitney *U* test, Chi-square test or Fisher's exact test as appropriate. P values were corrected for multiple comparisons by applying a Bonferroni correction for the three brain regions in DAT binding and for the nine results of symptom scales and questionnaires. One-way ANOVA was used to investigate differences in DAT binding between SPECT systems. Levene's test was used to test the equality of variances. Tukey's HSD test was used to correct for multiple comparisons in the ANOVA. Kruskal-Wallis test was used to investigate differences in occipital binding between vascular parkinsonism patients, other patients and healthy controls. The correlations were analyzed with Spearman's rank-correlation coefficients or Pearson's partial correlation coefficients, as appropriate. The level of statistical significance was set at $P < 0.05$.

3. Results

Demographic and clinical characteristics are presented in Table 1. Compared to healthy individuals, patients had more motor and non-motor symptoms and lower MMSE scores, and they reported higher levels of depression and anxiety (Table 1' Fig. 1). Posterior putamen DAT binding was 8.6% higher in patients than in controls ($p = 0.01$, Bonferroni corrected $p = 0.03$, Table 1' Fig. 1). When healthy subjects were

Table 1
Demographic and clinical characteristics of nondegenerative parkinsonism patients compared to healthy individuals.

Variable group	Variable	Patients	Healthy subjects	P value[1]	P value corrected[2]
Demographics	n	69	40	–	–
	Age (years)	65.5 (10.7)	66.8 (9.0)	0.99	–
	Sex (m/f)	34/35	21/19	0.75	–
Motor symptoms	MDS-UPDRS motor score	37.1 (15.0)	6.6 (5.5)	<0.001	<0.001
Premotor and non-motor symptoms	NMSS total score	67.8 (53.9)	16.2 (16.5)	<0.001	<0.001
	RBD (yes/no)	13/51	5/35	0.31	1.00
	Constipation	1.4 (3.2)	0.5 (1.5)	0.22	1.00
	Hyposmia	2.2 (3.7)	0.3 (1.4)	0.002	0.02
Cognition	MMSE	26.3 (2.6)	28.0 (2.1)	<0.001	<0.001
Mood and impulsivity	BDI	8.5 (8.1)	2.6 (3.9)	<0.001	<0.001
	BAI	11.8 (7.6)	4.2 (4.4)	<0.001	<0.001
	BIS11-total	60.4 (7.5)	56.8 (6.0)	0.02	0.14
DAT binding	Caudate	2.74 (0.43)	2.58 (0.32)	0.04	0.13
	Anterior putamen	2.65 (0.39)	2.49 (0.33)	0.03	0.08
	Posterior putamen	2.37 (0.38)	2.18 (0.32)	0.01	0.03

Values are means (SD) or n. Numbers of missing values: UPDRS = 1, RBD = 5, NMSS total score = 2, Constipation = 2, Hyposmia = 2, MMSE = 1, BDI = 7, BAI = 18, BIS11-total = 20. [1]Mann-Whitney *U* test, independent samples *t*-test or Chi-Square test. [2]Bonferroni correction to adjust for multiple comparisons for three DAT binding regions and for nine symptom scales and questionnaires.

divided into two groups based on posterior putamen SBR (20 subjects with the highest SBRs and 20 subjects with lowest SBRs) and compared, no differences in motor or non-motor symptoms were observed between the groups ($p > 0.40$).

DAT binding correlated negatively with age in both healthy controls (posterior putamen; $r = -0.33$, $p = 0.04$) and patients (all regions; $r = -0.29$ to -0.39, $p < 0.02$) but did not correlate with MDS-UPDRS motor score, MMSE or BDI ($r = -0.06$ to 0.22, $p > 0.12$), even when age was used as a covariate ($r = -0.01$ to 0.27, $p > 0.10$) (Fig. 2). Also, MDS-UPDRS motor score did not correlate with contralateral posterior putamen SBR in patients with asymmetrical symptoms ($r = 0.1$, $p = 0.53$, $n = 45$).

The average clinical follow-up time for symptomatic patients was 43.6 ± 19.3 months after imaging, and the final clinical diagnoses included ET, DIP or VP ($n = 46$) and other nondegenerative diagnoses, such as dystonia, functional movement disorder and depression (total $n = 23$). In subgroup analyses of ET, DIP and VP patients, ET patients had 10.2% higher SBRs in the posterior putamen compared to healthy controls ($n = 40$) ($p = 0.009$, Supplementary Table 1). No other significant subgroup differences were observed (Supplementary Table 1). There were no relevant differences in results obtained with different SPECT systems (Supplementary Table 2).

When healthy subjects with a positive family history of PD ($n = 6$) were excluded from the analysis, the difference between healthy controls and symptomatic controls increased (11.3% difference in the posterior putamen, $p = 0.002$, Bonferroni corrected $p = 0.006$). Also, when patients on SSRIs or SNRIs ($n = 10$) and patients with vascular ($n = 7$) or drug induced parkinsonism ($n = 12$) were excluded and the remaining patients were compared to healthy controls, results remained the same (8.7% difference in the posterior putamen, $p = 0.008$, Bonferroni corrected $p = 0.02$).

Posterior putamen dopaminergic asymmetry did not differ between the groups (healthy controls asymmetry index mean 0.005 (SD 0.06) vs symptomatic controls 0.03 (0.06), $p = 0.12$). No significant differences were found in occipital binding values between healthy controls and symptomatic patients (healthy controls mean (SD) counts-per-voxel value 36.8 (8.8) vs symptomatic controls 34.9 (7.3), $p = 0.24$). In addition, occipital binding was not affected in patients with vascular parkinsonism and no group differences were found between vascular parkinsonism patients (34.6 (7.2)), other patients (35.0 (7.3)) and healthy controls (36.8 (8.8) ($p = 0.60$). Patients with ET did not have significantly lower occipital binding values compared to healthy controls (ET 35.4 (7.4) vs healthy 36.8 (8.8), $p = 0.51$)

4. Discussion

The healthy individuals in our study had lower striatal DAT binding than a group of patients with motor symptoms. The paradoxical finding demonstrates that a selection of controls after diagnostic imaging may lead to an error if diagnoses are dependent on the imaging result. The results bear relevance for neuroimaging trials that use symptomatic patients as controls.

Diagnostic DAT imaging heavily directs clinical diagnosis: a symptomatic patient with abnormal DAT binding is likely to receive a diagnosis of degenerative parkinsonism syndrome (Ba and Martin, 2015; Mirpour et al., 2018). The Movement Disorder Society (MDS) clinical diagnostic criteria for PD support this view, as a normal presynaptic dopaminergic imaging finding has been listed as an exclusion criterion for PD diagnosis (Postuma et al., 2015). Therefore, if patient control groups are selected on the basis of nondegenerative diagnoses that are dependent on DAT imaging, this could thus result in a dopaminergically overly healthy group of patients, whereas unselected healthy controls also include individuals with borderline abnormal DAT binding. This limitation is particularly present in retrospective studies that use clinical diagnostic images of PD patients that are compared to normal images from other patient groups (termed clinically uncertain parkinsonism syndrome, CUPS).

It is also possible that control subjects with prodromal hypodopaminergic conditions volunteer more actively for neuroimaging trials than individuals without any symptoms (self-selection bias) (Hernán et al., Sep 2004). There are indications that volunteerism in positron emission tomography (PET) imaging studies is associated with higher levels of novelty seeking personality traits (Oswald et al., 2013), and individuals interested in brain MRI studies are more likely to be younger and to be men (Ganguli et al., 2015). On the other hand, in a study that focused on aging and cognition, volunteers were significantly more likely to be women and more educated (Ganguli et al., 1998). However, if this was the case in our study, one would have expected that healthy individuals with the lowest binding values would score higher in screens for prodromal or premotor symptoms of PD or in addiction/impulsivity-related tests. Since this was not the case, it seems unlikely that these subjects represent prodromal PD patients.

Although we consider methodological issues, particularly the selection of subjects as an important factor in the present results, we cannot exclude the possibility that group differences are partially driven by DAT upregulation in symptomatic patients. Evidence of DAT binding regulation suggests that binding is upregulated during amphetamine exposure due to increased extracellular dopamine, but downregulation of DAT is more often seen in pathological conditions (PD, attention deficit hyperactivity disorder (ADHD), bipolar disorder) and after longer use of amphetamine (Vaughan and Foster, Sep 2013). We thus consider DAT dysregulation as a possible but unlikely explanation of our findings. It should also be noted that MDS-UPDRS motor scores were relatively high also in ET patients which suggests that ET phenotypes were in many cases ET plus (Bhatia et al., 2018) and the pathophysiology of this phenotype could differ from typical cases of purely tremolous ET. In addition, although occipital values did not differ significantly between the groups, the mean values were slightly lower in symptomatic patients

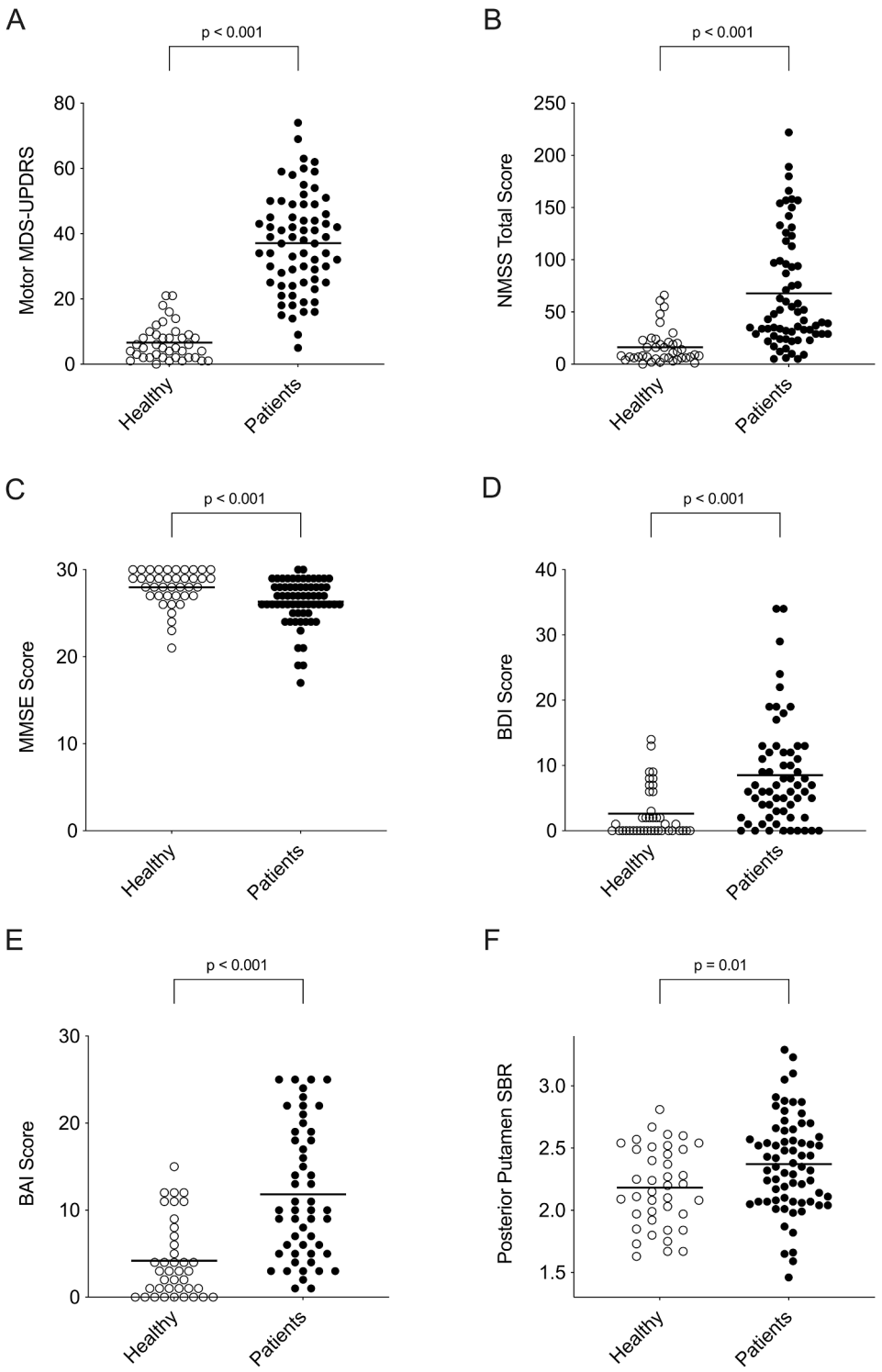

Fig. 1. Group differences. Differences in MDS-UPDRS part III (A), NMSS total scores (B), MMSE scores (C), BDI scores (D), BAI scores (E) and posterior putamen SBRs (F) between healthy volunteers and patients with nondegenerative parkinsonism or tremor.

as compared to healthy subjects (5.2%). As this region is used as the reference region in the analysis, and lower reference binding induces higher SBRs, it is possible that the results are a partial reflection of small changes in serotonin transporter (SERT) availability in the occipital region of symptomatic patients.

Our study was conducted with [^{123}I]FP-CIT SPECT and we cannot rule out that our results are specific for [^{123}I]FP-CIT SPECT. In addition, although this study included subjects scanned with three different systems, all SPECT devices were calibrated prior first study subject using a calibration procedure based on the work by Tossici-Bolt et al. (2011) and described in detail in the guidance by Hermes Medical Solution (Diemling, 2012). This calibration procedure has been carried out also in our earlier studies with different samples and systems and device-related difference have been tested in each study (see e.g. Kaasinen et al., 2014; Mäkinen et al., 2019; Jaakkola et al., 2019; Mäkinen et al., 2016; Jaakkola et al., 2017) with no statistically significant differences

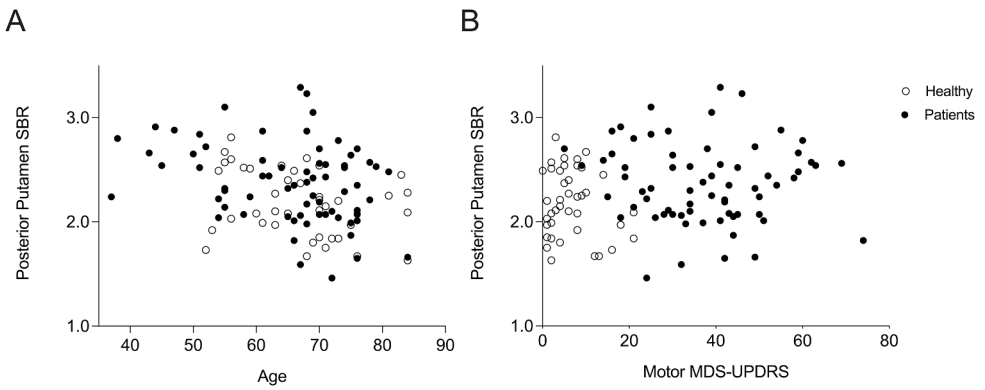

Fig. 2. DAT binding correlations. Significant correlation between age and posterior putamen DAT binding in patients (r = -0.29, p = 0.02) and healthy controls (r = -0.33, p = 0.04) (A). Nonsignificant correlation between motor symptom severity (MDS-UPDRS motor score) and posterior putamen DAT binding in patients (r = -0.06, p = 0.61) and healthy controls (r = 0.01, p = 0.97)(B).

between systems. Nevertheless, this issue is a major limitation of the study and underlines the need for a replication using other imaging systems.

To conclude, due to selection biases, patients with motor symptoms may have higher DAT binding compared to healthy subjects. Since the representativeness of control samples is critical for minimizing error and maximizing generalizability, the demonstrated effect should be taken into consideration when trials are designed and analyzed. Our results support the view that healthy controls are the most representative control group when the purpose is to model normality as opposed to pathology. Normality is likely best represented by healthy and asymptomatic subjects, although it is vitally important to understand the possibility of self-selection biases also in recruiting and selection of healthy controls.

CRediT authorship contribution statement

Emma A. Honkanen: Investigation, Formal analysis, Writing – original draft, Visualization. **Mikael Eklund:** Investigation, Formal analysis, Writing - review & editing. **Simo Nuuttila:** Investigation, Writing - review & editing. **Tommi Noponen:** Formal analysis, Writing - review & editing. **Elina Jaakkola:** Investigation, Writing - review & editing. **Elina Mäkinen:** Investigation, Writing - review & editing. **Risto Hirvilammi:** Formal analysis, Writing - review & editing. **Marko Seppänen:** Writing - review & editing. **Kari Lindholm:** Investigation, Writing - review & editing. **Filip Scheperjans:** Supervision, Writing - review & editing. **Riitta Parkkola:** Writing - review & editing. **Juho Joutsa:** Supervision, Writing - review & editing. **Andrea Varrone:** Supervision, Writing - review & editing. **Valtteri Kaasinen:** Conceptualization, Methodology, Validation, Investigation, Writing - review & editing, Visualization, Project administration.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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